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<p>(54) Title: ANALGESIC COMBINATIONS</p> <p>(57) Abstract</p> <p>A pharmaceutical composition for oral or rectal administration comprising as active agents a) hydroxyzine in free form or in pharmaceutically acceptable salt form, and b) one or more non-steroidal anti-inflammatory/analgesic agents and/or acetaminophen. These combinations are particularly useful in alleviating the symptoms of pain.</p>		

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ANALGESIC COMBINATIONS

The present invention relates to pharmaceutical compositions active as analgesics as well as to methods for alleviating the symptoms of pain.

Many individual agents and combinations are known for alleviating the symptoms of pain. The quest for agents and combinations which will  
5 optimise the therapeutic effect and minimise undesired side effects continues in an attempt to find improved treatments.

1-(p-chlorobenzhydryl)-4-[2-(2-hydroxyethoxy)ethyl]-diethylene-diamine (hereinafter Hydroxyzine) and salts thereof are known to be effective tranquilisers.

10 It has now surprisingly been found that co-administration of Hydroxyzine and salts thereof with acetaminophen has an advantageous analgesic effect. It has also more surprisingly been found that co-administration of Hydroxyzine and salts thereof with one or more non-steroidal anti-inflammatory/analgesic agents (also known as NSAIDs) has an especially  
15 advantageous analgesic effect. The invention is practised by administration adapted to achieve absorption through the alimentary canal, i.e. by oral or rectal administration, desirably by oral administration.

Accordingly, one aspect of the invention provides a pharmaceutical composition for oral or rectal administration comprising as active agents:

- 20 a) Hydroxyzine in free form or in pharmaceutically acceptable salt form, and  
b) one or more non-steroidal anti-inflammatory agent and/or acetaminophen.

Active agent a) is known and can be prepared e.g. as described  
25 in USP 2,899,436.

Any of a wide variety of non-steroidal, anti-inflammatory agents may be used as active agents b). Useful materials include aspirin; sodium 5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrole-2-acetate dihydrate (generically referred to as zomepirac sodium); 4-hydroxy-2-methyl-N-(2-  
30 pyridyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide (generic name



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Piroxicam); 2',4'-difluoro-4-hydroxy-3-biphenylcarboxylic acid (generic name Diflunisal); 1-isopropyl-7-methyl-4-phenyl-2 (1H)-quinazolinone (generic name Proquazone); and arylacetic acid or arylpropionic acid compounds including the non-toxic therapeutically acceptable salts thereof, e.g. the sodium, potassium or calcium salts. Examples of useful arylacetic acid and arylpropionic acid compounds include 2-(p-isobutylphenyl)propionic acid (generic name Ibuprofen); alpha-methyl-4-(2-thienylcarbonyl) benzene acetic acid (generic name Suprofen); 4,5-diphenyl-2-oxazole propionic acid (generic name Oxaprozin); rac-6-chloro-alpha-methylcarbazole-2-acetic acid (generic name Carprofen); 2-(3-phenyloxyphenyl)propionic acid, particularly the calcium salt dihydrate thereof (these compounds being referred to generically as Fenoprofen and Fenoprofen calcium); 2-(6-methoxy-2-naphthyl) propionic acid (generic name Naproxen; the generic name of the sodium salt is Naproxen sodium); 4-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)-alpha-methylbenzene acetic acid (generic name Indoprofen); 2-(3-benzoylphenyl) propionic acid (generic name Ketoprofen); and 2-(2-fluoro-4-biphenyl) propionic acid (generic name Flurbiprofen). 1-5-(4-Methylbenzoyl)-1H-pyrrole-2-acetic acid (generic name Tolmetin). All of the aforementioned non-steroidal, anti-inflammatory agents and their preparation are known. For example the synthesis of zomeriprac sodium, fenoprofen, indoprofen and ibuprofen is described in U.S. 4,242,519, U.S. 3,752,826, U.S. 3,228,831 and U.S. 3,385,886.

Acetaminophen and its preparation are also well known.

It is preferred that active agents a) and b) are the sole active analgesic constituents in the pharmaceutical combinations according to the invention. Preferred as active agent b) is a non-steroidal anti-inflammatory agent in particular one or more of those listed above.

It is also preferred that hydroxyzine be employed in the form of its hydrochloride or pamoate salt.



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The compositions according to the invention suitably contain pharmaceutically acceptable carriers or diluents which are admixed with the active agents and are conventional and well known in the art.

The compositions of this invention may be adapted for oral administration and administration through the rectum. Forms suitable for oral administration are for example tablets, dispersible powders, granules, capsules, syrups, elixirs or suspensions. Compositions for oral use contain one or more conventional adjuvants, such as sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide an elegant and palatable preparation. Tablets may contain the active ingredients in admixture with conventional pharmaceutically acceptable excipients, e.g. inert diluents, such as calcium carbonate, sodium carbonate, lactose, and talc, granulating and disintegrating agents, e.g. starch and alginic acid, binding agents, e.g. starch gelatin and acacia, and lubricating agents, e.g. magnesium stearate, stearic acid and talc. The tablets may be uncoated or coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. Similarly, suspensions, syrups and elixirs may contain the active ingredients in admixture with any of the conventional excipients utilized in the preparation of such compositions, e.g. suspending agents such as methyl-cellulose, tragacanth and sodium alginate; wetting agents such as lecithin, polyoxyethylene stearate and polyoxyethylene sorbitan monooleate; and preservatives such as ethyl p-hydroxybenzoate. Capsules may contain the active ingredients alone or admixed with an inert solid diluent, e.g. calcium carbonate, calcium phosphate and kaolin. These pharmaceutical compositions may contain up to about 90% of the active ingredients in combination with the carrier or adjuvant. Preferably the compositions are put up in unit dosage form particularly in unit dosage form for oral administration. Such forms may contain the active ingredients separately, e.g. in separate layers in a layer or mantle tablet or in split capsules. Oral administration is preferred.



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A further aspect of the invention concerns a process for the production of a pharmaceutical composition as stated above which comprises formulating active agent a) with active agent b) as stated above and optionally putting up the preparation in unit dosage form.

- 5 A clinical test was conducted involving subjects who were outpatients undergoing the surgical removal of impacted teeth. After surgery was completed, the patients were given one dose of a medication and a questionnaire. They were asked to take the medication when their post-operative pain reached moderate to severe intensity. They were instructed
- 10 to record their starting pain level in numerical fashion, i.e., moderate (2) or severe (3) and then at each hour for the next four hours to record their pain intensity as severe (3), moderate (2), slight (1), or none (0); and their relief from the starting pain as complete (4), a lot (3), some (2), a little (1) or none (0). The procedure employed is state-of-the-art
- 15 methodology and is described in more detail in an article entitled "A Model to Evaluate Mild Analgesics in Oral Surgery Out-patients", S.A. Cooper and W.T. Beaver, Clinical Pharmacology and Therapeutics, Vol., 20, Number 2, pp. 241-250, August, 1976.

In the test, the patients were given a placebo, 600 milligrams of

20 acetaminophen, 100 milligrams of Hydroxyzine pamoate, or a mixture of 100 milligrams of Hydroxyzine pamoate and 600 milligrams of acetaminophen.



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The results of the test are recorded in Table 1 below. Pain intensity difference scores were derived by subtracting the pain level at each hour after ingestion from the intensity at the time of initial administration. Hence if the patient's pain was judged to be "moderate" (value of 2) at the start of the test and the patient judged his pain to be "slight" at hours one, two, three and four (assigned value of 1), the pain intensity difference score would be 4, that is 2 minus 1 or plus 1 at each of the four hourly measuring points. Pain relief scores for each pain estimate were assigned according to patient's hourly estimate of relief. Accordingly, if the patient recorded a little relief at hour one into the test (a score of 1) and some relief at hour two (a score of 2) and a lot of relief at hours three and four (score 3 for each hour) his pain relief score would be 9.

TABLE 1

	<u>Placebo</u>	<u>Acetaminophen 600 mg</u>	<u>Hydroxyzine Pamoate 100 mg</u>	<u>Hydroxyzine 100 mg + Acetaminophen 600 mg</u>
15				
20				
Number of Patients	6	7	4	6
Mean Sum Pain Intensity Difference Score	-0.17	3.14	-0.50	4.50
25				
Mean Sum Pain Relief Score	4.00	8.14	3.00	10.83

In a second test series, periodontal patients, after completion of surgery, were tested using the above procedures except that they were requested to record pain intensity and pain relief levels at 30 minutes, and then at each hour for the next 4 hours. The test scores are therefore the sum of five readings rather than 4 readings as in the above test. In this test the patients were given 100 mg of Hydroxyzine pamoate, 400 mg ibuprofen or a mixture of 100 mg hydroxyzine pamoate with 400 mg of ibuprofen.



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RESULTSTABLE 2

	Hydroxyzine Pamoate 100mg	Ibuprofen 400mg	Combined
5 Number of Patients	12	13	11
Mean Sum Pain Intensity Difference Score	0.33	6.69	7.73
10 Mean Sum Pain Relief Score	2.17	13.54	14.73

The data obtained from this second test when plotted showed at the end of 4 hours that the line of the curve for the combination was continuing essentially horizontally whereas the line for Ibuprofen alone was declining at an angle of about 20°.

- 15 In a third test series, oral surgery patients, after completion of surgery, were tested using the same procedures except that they were requested to record pain intensity and pain relief levels at 30 minutes and then at each hour for the next six hours. The test scores are therefore the sum of seven readings rather than four readings as in the
- 20 first test. In the tests, the patients were given a placebo, 200 milligrams of fenoprofen calcium, 100mg of hydroxyzine pamoate or a mixture of 100mg of hydroxyzine pamoate with 200 mg of fenoprofen calcium. The test data are shown in Table 3 below.

TABLE 3

	Placebo	Hydroxyzine Pamoate 100 mg	Fenoprofen Calcium 200 mg	Hydroxyzine Pamoate 100 mg + Fenoprofen Calcium 200 mg
25 Number of Patients	9	11	11	10
30 Mean Sum Pain Intensity Difference Score	1.56	1.50	3.55	9.60
35 Mean Sum Pain Relief Score	8.33	3.25	12.00	18.40





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Thus the above tests indicate a synergism of the potentiating kind for the combination of active agent a) with an active agent b).

They also confirm literature studies indicating that hydroxyzine alone is inactive orally as an analgesic.

- 5       The combination is thus indicated for use in alleviating the symptoms of pain.

Accordingly the invention further provides a method of alleviating the symptoms of pain in a subject in need of such treatment, which method comprises concomitantly administering to said subject an  
10   effective amount of an active agent a) and an active agent b) as stated above.

It has also been determined that co-administration of active agents a) and b) does not possess the nausea-causing properties normally associated with analgesic combinations. Co-administration of active agents  
15   a) and b) also exhibits anti-emetic and anti-histaminic effects.

The therapeutic dose differs with the kind of pharmaceutical process, severity of the condition, administration schedule and other known factors when co-administration is envisaged, and doses typically continued until the condition causing the pain is ameliorated. Usually, the NSAID or  
20   acetaminophen will be co-administered with a pain relieving potentiating effective amount of hydroxyzine (or its salts), in a total combined pain relieving effective amount, in doses given 3 to 6 times a day as needed to relieve pain. In general, at least 25 mg of hydroxyzine and its salts will be administered per dose, preferably at least 50 mg and typically  
25   at least 70 mg. A dose for each administration of hydroxyzine and its salts may range from 25 mg to 120 mg, more usually 25 mg to 100 mg, preferably 50 mg to 100 mg, and typically 70 mg to 100 mg. The amount of the non-steroid anti-inflammatory agent to be co-administered with the hydroxyzine will vary depending mainly on the particular agent  
30   desired. In general, it is desirable to employ at least an amount of the NSAID (or acetaminophen when it may be used) that would by itself be minimally effective clinically in the adult human to produce analgesia.



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The particularly preferred NSAIDs are those classed as arylacetic and arylpropionic acids (and the pharmaceutically acceptable salts) including, for example, ibuprofen, oxaprozin, carprofen, fenoprofen or fenoprofen calcium, naproxin or naproxin sodium, indoprofen, ketoprofen, flurbiprofen and tolmetin or tolmetin sodium. Also of particular interest are the NSAIDs proquazone, zomepirac, piroxicam and diflunisal.

In Table I, below, there are given various NSAIDs of particular interest along with general (a), preferred (b) and in some cases more preferred (c) milligram dose ranges for each administration (column A); the weight ratio thereto of hydroxyzine when the hydroxyzine dose to be administered is within the range of 25 to 100 mg (Column B); and the weight ratio thereto of hydroxyzine when the hydroxyzine dose to be administered is within the range of 50 to 100 mg (Column C).

Suitable doses for acetaminophen are from 200-1,300 mg, preferably 300-650 mg, leading to the same weight ratios with hydroxyzine (25 to 100 mg range and 50 to 100 mg range) as indicated for aspirin in Table I.

The limits of weight ratio ranges of hydroxyzine for the hydroxyzine dose ranges of 25 to 120 mg and 70 to 100 mg, to the dose ranges for NSAIDs given in Table I may be readily calculated from the dose ranges given in Column A of Table I for the particular NSAID (as well as from the above information for acetaminophen), and such weight ratio ranges are also deemed disclosed herein. It will be evident that the weight ratio ranges of hydroxyzine to the NSAID or acetaminophen as indicated above may be used to formulate pharmaceutical compositions in accordance with the invention, provided that a NSAID or acetaminophen pain relieving potentiating effective amount of hydroxyzine is included.



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	Column A	Column B	Column C
	NSAID dose range	Weight ratio hydroxyzine range at 25-100 mg to NSAID dose range	Weight ratio hydroxyzine range at 50-100 mg to NSAID dose range
NSAID Ibuprofen	a) 100-800 b) 150-600 c) 200-400	1:32 to 1:1 1:24 to 1:1.5 1:16 to 1:2	1:16 to 1:1 1:12 to 1:1.5 1:8 to 1:2
Oxaprozin	a) 300-1200 b) 400-800	1:48 to 1:3 1:32 to 1:4	1:24 to 1:3 1:16 to 1:4
Carprofen	a) 50-400 b) 100-300	1:16 to 1:0.5 1:12 to 1:1	1:8 to 1:0.5 1:6 to 1:1
Fenoprofen or Fenoprofen calcium	a) 50-600 b) 100-400 c) 150-300	1:24 to 1:0.5 1:16 to 1:1 1:12 to 1:1.5	1:12 to 1:0.5 1:8 to 1:1 1:6 to 1:1.5
Naproxen or Naproxen sodium	a) 100-600 b) 200-400	1:24 to 1:1 1:16 to 1:2	1:12 to 1:1 1:8 to 1:2
Indoprofen	a) 25-200 b) 50-150	1:8 to 1:0.25 1:6 to 1:0.5	1:4 to 1:0.25 1:3 to 1:0.5
Ketoprofen	a) 25-300 b) 50-200	1:12 to 1:0.25 1:8 to 1:0.5	1:6 to 1:0.25 1:4 to 1:0.5
Flurbi- profen	a) 15-200 b) 25-150	1:8 to 1:0.15 1:6 to 1:0.25	1:4 to 1:0.15 1:3 to 1:0.25
Zomepirac	a) 15-200 b) 25-100	1:4 to 1:0.15 1:4 to 1:0.25	1:2 to 1:0.15 1:2 to 1:0.25
Piroxicam	a) 10-50 b) 15-37.5	1:2 to 1:0.1 1:1.5 to 1:0.15	1:1 to 1:0.1 1:0.75 to 1:0.15
Diflunisal	a) 125-1000 b) 250-750	1:40 to 1:1.25 1:30 to 1:2.5	1:20 to 1:1.25 1:15 to 1:2.5
Proquazone	a) 60-300 b) 75-150	1:2 to 1:0.6 1:6 to 1:0.75	1:6 to 1:0.6 1:3 to 1:0.75
Aspirin	a) 200-1300 b) 300-650	1:52 to 1:2 1:26 to 1:3	1:26 to 1:2 1:13 to 1:3
Tolmetin or Tolmetin sodium	a) 300-800 b) 400-600	1:32 to 1:3 1:24 to 1:4	1:16 to 1:3 1:12 to 1:4



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Conveniently the active agents will be administered in fixed combinations having e.g. the individual dosages outlined above and in unit dosage form.

They can be administered e.g. in sustained release form or in  
5 divided doses 2 to 4 times a day or as indicated by the condition to be treated e.g. 3 to 6 times as needed to relieve pain.

The active agents a) and b) can also be administered e.g. in the indicated dosages individually and concomitantly.

The invention therefore also provides a pack comprising separately  
10 a plurality of dosage units of each of active agents a) and b) together with instructions for their concomitant administration.

The following Examples are illustrative of compositions for use in the invention.



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Example A

A No. 1 capsule containing the ingredients indicated below may be prepared by conventional techniques and administered at a dose of 1 or 2 capsules 4 to 6 times a day to relieve pain.

	<u>Ingredient</u>	<u>Weight (mg)</u>
5	Ibuprofen	200
	Hydroxyzine pamoate	50
	Corn starch	150
	Magnesium stearate	2

Example B

10 A tablet containing the ingredients indicated below may be prepared by conventional techniques and administered at a dose of 1 or 2 tablets 3 to 5 times a day to relieve pain.

	<u>Ingredient</u>	<u>Weight (mg)</u>
	Proquazone (micronized)	75
15	Hydroxyzine hydrochloride	25, 50 or 75
	Lactose powder	279.2
	Alginic acid	90
	Yellow iron oxide (T-1624)	1.5
	Celloidal silicon dioxide	13
20	Pluronic F-68	1.3
	Poridone	10
	Stearic acid	5

Using a single dose tablet containing 75 mg of hydroxyzine hydrochloride and formulated as in Example B (75 mg of proquazone), and  
25 administered in a clinical test as described above, indicated after 6 hours a clear potentiation of the pain relieving effects of proquazone by the hydroxyzine.



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WE CLAIM

1. A pharmaceutical composition for oral or rectal administration comprising as active agents
  - a) Hydroxyzine in free form or in pharmaceutically acceptable salt form, and
  - 5 b) one or more non-steroidal anti-inflammatory/analgesic agents and/or acetaminophen.
2. A composition according to Claim 1 wherein agent b) is a non-steroidal anti-inflammatory drug.
3. A composition according to Claim 2 wherein agent b) is selected  
10 from
  - (i) ibuprofen, oxaprozin, carprofen, fenoprofen or fenoprofen calcium, naproxin or naproxin sodium, indoprofen, ketoprofen, flurbiprofen and tolmetin or tolmetin sodium or
  - (ii) proquazone, zomepirac, piroxicam and diflunisal.
- 15 4. A composition according to any one of the preceding claims wherein Hydroxyzine is present in the form of its hydrochloride or pamoate.
5. A composition according to any one of the preceding claims in unit dosage form.
6. A composition according to any one of the preceding claims wherein  
20 active agent a) is present in an amount sufficient to potentiate the analgesic effect of active agent b).
7. A preparation according to anyone of the preceding claims containing 25 to 120 mg of hydroxyzine or the hydrochloride or pamoate thereof.
8. A process for the production of a pharmaceutical composition  
25 according to Claim 1 which comprises formulating active agent a) with active agent b).



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9. A composition according to any one of Claims 1 to 7 for use in alleviating the symptoms of pain.

10. A method of alleviating the symptoms of pain, which comprises co-administering to a subject a potentiating effective amount of active agent b) each as defined in Claim 1.

11. A pack comprising separately a plurality of dosage units of each of active units a) and b) together with instructions for their concomitant administration.

